The Sapphire Group™

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Creosote Council II

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**SUBJECT:** Critique of USEPA's Creosote Human Risk Characterization

## 1.0 INTRODUCTION

*The Sapphire Group, Inc.* has carried out a critical review of USEPA's Creosote Human Risk Characterization (USEPA, 2003). EPA's risk assessment indicates that high, unacceptable cancer and non-cancer regulatory risks from dermal and inhalation exposure to creosote exists for all creosote workers. Our review has identified and focused on the issues and assumptions that afford the greatest impacts on the quantitative estimates of hazard and risk provided by the USEPA. Other considerations will also influence the outcome, although perhaps to a lesser degree; and their basis and influence ought to be examined more carefully during the review and comment period since the cumulative effect on the final risk estimate may be substantial when all such variables are considered together.

This evaluation provides comments on the cancer and non-cancer key issues organized into three sections: Hazard Identification, Toxicity Assessment, and Exposure Assessment. Within each section, the approach taken by USEPA is first summarized followed by comments and recommendations from *The Sapphire Group, Inc.*. These comments, suggestions, and evaluations are offered in the hope that they can serve as a starting point in a technical discussion to improve the reliability and validity of the risk estimates by replacing certain assumptions currently made by EPA and by better characterizing the uncertainty surrounding the creosote risks to workers.

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## 2.0 HAZARD IDENTIFICATION

**USEPA Approach:** Benzo(a)pyrene (B(a)P) was identified as an indicator chemical for carcinogenic risks posed by creosote, assuming a content of 0.5% in creosote. Naphthalene was identified as an indicator chemical for non-cancer hazards. No other chemicals were addressed.

**Comment:** Predicting the toxicity of a complex mixture like creosote on the basis of one of its components is likely to be misleading, because the interactions among the components may modify toxicity. Since polynuclear aromatic hydrocarbons (PAHs) require metabolic activation by mono-oxygenases to elicit carcinogenic effects, any alteration in these metabolic pathways will influence the observed toxicity. There are two primary mechanisms by which chemicals interact with PAHs to influence toxicity. A compound may compete for the same metabolic activating enzymes and thereby reduce the toxicity of carcinogenic PAHs, or it may induce the metabolizing enzyme levels to result in a more rapid detoxification of the carcinogenic PAHs (Levin *et al.*, 1982). Alternatively, compounds may compete for a deactivating pathway, thereby increasing the toxicity of PAHs (Furman *et al.*, 1991). USEPA's approach is, therefore, overly simplistic for such a complex mixture as creosote and cannot reliably address possible interactions with the other constituents, which can result in additive, independent, synergistic, or antagonistic effects (Gaylor *et al.*, 1999). As such, it may overstate or understate the true risk, and no way exists to determine the significance of this area of uncertainty from the information provided in the Agency's documentation.

The interaction between non-carcinogenic and carcinogenic PAHs has been extensively examined in animals. Administration of various combinations of polyaromatic hydrocarbons (PAHs) in mostly dermal animal experiments has resulted in synergistic as well as an additive or inhibitory effects compared to the carcinogenic action of the separate compounds, without any consistency as to the type of compounds used. Non-carcinogenic PAHs have exhibited co-carcinogenic potential and tumor-initiating and promoting activity when applied with B(a)P to the skin of mice (Van Duuren and Goldschmidt 1976; Van Duuren *et al.*, 1973). The synergistic effect of individual PAHs on the mutagenicity of B(a)P has also been demonstrated (Baird *et al.*, 1984). Chaloupka *et al.* (1993) showed that a mixture of PAHs, produced as by-products from a manufactured gas plant, was 706 times more potent than expected, based on its B(a)P content (0.17%) at inducing mouse hepatic microsomal ethoxyresorufin O-deethylase. Several other experiments, however, have shown that most PAH mixtures are considerably less potent than individual PAHs. Interactions between selected

non-carcinogenic PAHs and carcinogenic B(a)P have reduced the carcinogenic potential of B(a)P in animals (Falk *et al.*, 1964). Phenanthrene administration with B(a)P decreased the DNA adduct formation in mice (Rice *et al.*, 1984) and benz[a]anthracene may serve as an anti-carcinogen when administered with B(a)P (Smolarek *et al.*, 1986). B(a)P and dibenz[a,h]anthracene in combination with 10 non-carcinogenic PAHs were less potent tumor-inducers than was dibenz[a,h]anthracene alone or in combination with B(a)P (Pfeiffer,1977). Phenanthrene, a non-carcinogenic PAH, demonstrated a dose-related inhibition of dibenz[a,h]anthracene-induced carcinogenicity in mice (Falk *et al.*, 1964). Various combustion emissions and B(a)P have been examined for carcinogenic potency and tumor initiation activity on mouse skin. In all cases, PAH mixtures were much less potent than B(a)P alone (Slaga *et al.*, 1980). One study demonstrated that the relative tumorigenicities, as compared to B(a)P, of automobile exhaust condensate (AEC), diesel emission condensate, and a representative mixture of carcinogenic PAHs were 0.0053, 0.00011, and 0.36, respectively, following chronic application to mouse skin (Misfeld, 1980). AEC has also exhibited an antagonistic influence on B(a)P carcinogenicity when subcutaneously administered to mice; this effect was particularly augmented at higher B(a)P concentrations (Pott *et al.*, 1977). Carcinogenic and non-carcinogenic PAHs, comprising a quantitative fraction of automobile exhaust gas condensate, were selected for carcinogenicity testing via dermal exposure of female NMRI mice. The purpose was to identify interactions between mixtures of the carcinogenic and non-carcinogenic PAHs (Schmahl *et al.*, 1977). Treatment was carried out twice a week, for the natural lifetime of the animals. Although the carcinogenic action observed could be attributed almost entirely to the action of the carcinogenic PAHs, in relatively small doses, addition of the non-carcinogenic PAHs did not inhibit carcinogenesis, but had an additive effect. The dermal absorption of B(a)P was measured in the presence or absence of complex organic mixtures derived from coal liquefaction processes (Dankovic *et al.*, 1989). The dermal half-life of B(a)P was 3.0 hours when applied alone, 6.7 hours when measured as a component of a mixture, and ranged from 7.8 to 29.7 hours in the presence of different mixtures. The authors proposed that these mixtures inhibit the dermal absorption of B(a)P by inhibiting the metabolism of B(a)P at the application site. Such interactions play important modulatory roles in the expression of PAH toxicity of a mixture like creosote that may not be adequately reflected based on the toxicity of a single PAH like B(a)P.

Several possible options exist to resolve this issue. Theses include the following:

1) Refine the creosote risk assessment for the existing indicator chemicals

2) Expand the creosote risk assessment to include other key PAH components of creosote as well as other compounds in the mixture
3) Develop the risk assessment using a creosote (or closely related substance) mixture itself.

Of these, we believe that refining the risk assessment based upon B(a)P and naphthalene alone or expanding it to include additional surrogate compounds will not be sufficient to accurately assess the potential risk to creosote workers. We recommend replacing this approach with the third option: a mixtures risk assessment (surrogate approach) (USEPA, 2002a). The impact of this change will depend largely upon results of a revised toxicity assessment, but it is the best option for regulatory purposes in order to avoid under or over-estimating creosote risks, and employing other conservative, but unsupported, assumptions as a means of off-setting an assumed underestimation of risk.

Characterization of the variation in the PAH content of creosote mixtures should be performed as a first step to address the uncertainty associated with using toxicity results obtained from a single creosote mixture study as representative of all possible mixtures. The Creosote Council has such data, and has made them available to USEPA to assist in such a refinement. Furthermore, a relatively robust literature on creosote and related mixtures toxicity (cancer and non-cancer) could be employed to obtain a clearer understanding of the nature and magnitude of th hazard potential for occupational and non-occupational exposure of such mixtures.

## 3.0 TOXICITY ASSESSMENT

**USEPA Approach:** For cancer risk assessment, USEPA adopted the oral slope factor of 7.3 $(mg/kg\text{-}day)^{-1}$ for B(a)P, to be applied for all routes of exposure. For non-cancer assessment, USEPA adopted the inhalation RfC of 0.003 $mg/m^3$ for naphthalene.

**Comment:** USEPA's approach is oversimplified, in that the same slope factor is applied to <u>all</u> routes of exposure. Since the principle tumors for B(a)P exposure occur at the point of contact, this approach essentially assumes that the skin, gastrointestinal tract, and respiratory tract are the same with respect to chemical absorption, metabolism, and repair mechanisms. This assumption is <u>not</u> valid. Furthermore, the dose used for characterizing dose-response (mg/kg-day) is potentially inappropriate for point-of-contact tumors, since tumor formation is controlled by local tissue factors and, therefore, is <u>not</u> related to systemic dose. A surface area dose should be utilized in this case.

USEPA's RfC for naphthalene (0.003 $mg/m^3$) also differs considerably from ACGIH's TLV of 10 ppm (52.4 $mg/m^3$). USEPA applied an uncertainty factor (UF) of 3000 (10 for interspecies variation, 10 for sensitive human subpopulations, 10 for use of a LOAEL, and three for insufficiency in the database), which is the maximum value allowable for an uncertainty factor under current guidelines. Maximizing the UFs seems inappropriate for all the underlying uncertainties and ought to be re-examined. Assessment of dose-response for a chemical's toxicity requires both (1) estimating the degree of injury that a chemical may impart (*i.e.*, poisoning) to an individual or a population and (2) estimating dose ranges in which no toxic injuries are likely to occur. In practice, this is largely a process that translates the toxic potency of a substance as defined by high-dose, laboratory animals studies to the toxic potency for humans exposed to lower (often considerably lower) doses experienced by humans. Two main steps are involved in this process:

1) Extrapolation from a test species to humans to take into account quantitatively the degree of variability in susceptibility that may exist between humans and other species; and

2) Extrapolation from the high doses administered to laboratory animals and the lower doses experienced by humans in assorted situations (*e.g.*, workplace vs. home).

The tools to accomplish these applications to humans for non-carcinogens are the uncertainty factors (UF) with a range of one to ten being applicable to each form of extrapolation. The National Academy of Sciences (NAS/NRC), the World Health Organization (WHO), and USEPA have all commented on the use of UFs in the recent past. In the opinion of these organizations and of outside experts, UFs can and should accommodate a wide continuum of numerical expressions other than a single default value (most notably, 10). The NAS/NRC has stated, "*There is no strong scientific basis for using the same constant uncertainty factor for all situations...*" (NRC, 1994). With the growing support for chemical-specific of data-driven uncertainty factors in non-cancer risk assessment, which incorporate toxicokinetic and toxicodynamic data, the application of uncertainty factors other than three or 10 has (and should) become more frequent in human health risk assessment (IPCS, 2001; USEPA, 2002b). As early as 1978, WHO deliberated on the magnitude of UFs and recognized the value of a continuum by noting that "a factor of two to five may be considered sufficient if the effects against which individuals or a population are to be protected is not regarded as very severe." WHO (1999) has since

reinforced the use of one UF for each extrapolation; however, it went further in parsing out quantitatively a toxicodynamic and a toxicokinetic consideration for each. Since its inception, USEPA has attempted to systematically structure the use of UFs, and increasingly has moved away from their rigid application of default values. As a demonstration that each UF is indeed a continuum whereby a value is selected based on factual understanding of toxicity, when deriving an oral RfD for boron, USEPA recently adopted a set of chemical-specific uncertainty/variability factors of 4.08, 1.6, 2.5, 1.2, and 3.16 to yield a net uncertainty factor of 61.9 (USEPA, 2001). A similar approach was adopted by IPCS in their assessment of boron as well (IPCS,1998). The selection and use of UFs in the non-cancer risk assessment of creosote requires careful evaluation.

Defensible options for an improved toxicity assessment of creosote include the following:

1) Refine the cancer slope factor for B(a)P and the RfC/RfD for naphthalene using the most recent guidelines for cancer and non-cancer assessment (USEPA, 1999; USEPA, 2002b). There are several sources of non-linearity (saturable metabolism, enzyme induction, saturable DNA repair processes) that affect high-to-low dose extrapolation, and are not considered in the existing value (or the draft creosote risk assessment as a consequence). Species differences for these factors are likely to exist. Furthermore, differences between skin and the forestomach with respect to absorption and metabolic activation of B(a)P could also be addressed. Physiologically-based-pharmacokinetic (PBPK) models and kinetic data are available for PAHs including B(a)P and naphthalene (Roth and Vinegar, 1990; Withey *et al.*, 1991, 1993, 1994; Sweeney *et al.*, 1996; Gautier *et al.*, 1996; Moir *et al.*, 1998; Viau *et al.*, 1999) that could address some of these extrapolation and scaling issues to provide a sounder basis for decision-making.

2). Derive an oral slope factor for creosote based upon oral bioassays (*i.e.*, Culp *et al.*, 1998). This study provides an excellent characterization of the dose-response relationship for coal tar and tumors in mice across a broad range of doses.

3). Derive dermal slope factor for creosote based upon an as yet unidentified dermal bioassay. If high quality studies exist, they would be more directly relevant to the occupational scenario of interest.

4). Define an RfC/RfD for creosote mixtures using alternative uncertainty factor values.

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5. Refine the RfC for naphthalene using benchmark dose methods and alternative uncertainty factor values.

Consistent with our recommendation for the Hazard Identification step, we recommend replacing the oral potency for B(a)P with an oral potency factor derived for creosote (option 2). This is done in the absence of an adequate dermal cancer study and is consistent with the approach taken by USEPA in their draft creosote risk assessment. The coal tar bioassay of Culp *et al*. (1998) is well designed to assess dose-response relationships and sufficiently similar to creosote to be useful in assessing the risks of the mixture. Other oral or dermal bioassays not yet retrieved or reviewed may provide additional support for this approach as well as address the issue of the variability of the mixture (*i.e.*, consistency of response). A preliminary analysis of the Culp *et al.* data suggests that the dose-response relationship for coal tar (and likely for creosote as well) is non-linear at low doses (**Figure 1**), consistent with the hypothesized sources of non-linearity listed above. Preliminary potency estimates from this study suggest that the risk estimates calculated by USEPA based upon B(a)P alone will be approximately **27- to 300-fold** lower when the mixture is assessed per current guidelines. Use of other studies, a meta-analysis of several studies, or probabilistic modeling of the cancer potency may provide better numbers or support for the potency factor derived from the Culp *et al.* (1998) study. Review of the published (and unpublished) literature for high quality dermal cancer bioassays of creosote should be considered before this approach is abandoned entirely.

Option 5 is rejected for the some reason as was Option 1. There are sufficient high quality data from which an RfC and RfD can be derived for "creosote," and a novel RfC and RfD should, therefore, be developed and used for the mixture in assessing worker risks. Two 90-day inhalation studies of creosote have been provided for review and derivation of a "creosote" RfC (Hilaski, 1995c, 1995d), which would be superior to that derived for naphthalene for purposes of assessing non-cancer risk from creosote exposure. Even if the naphthalene is used for this purposes, there is some room (**~3-to 30-fold**) for improvement in the default uncertainty factor value selection made based on careful review and discussion of the UFs involved. A dermal RfD for creosote can also be derived using two 90-day studies dermal studies of creosote (Hilaski, 1995a, 1995b) and applying appropriate UFs. The same critical review of UF selection should be applied to a *de novo* RfC and RfD for creosote. An avenue of investigation that prove fruitful in more accurately defining risks is the potential species differences between rodents and humans using nasal dosimetry and the Sweeney *et al.* PBPK model for naphthalene and other creosote components.

## 4.0 EXPOSURE ASSESSMENT

**USEPA Approach:** USEPA used the Bookbinder (2001) data for occupational exposure scenarios **1a** (treatment operator) and **1b** (treatment assistant). All other occupational scenarios (paint brush liquid application, mop liquid application, paint brush grease application, injector grease application) were based upon default assumption obtained from the Pesticide Handlers Exposure Database (PHED version 1.1). Criticisms in the Bookbinder (2001) study were raised, and included: (1) no attempt to relate inhalation levels of PAHs and coal tar pitch volatiles (CTPVs) to total creosote; (2) calculation mistakes with the inhalation data; (3) inconsistencies with raw data and bar graphs; and (4) low inhalation recoveries of 51-57%. These criticisms have been addressed elsewhere. USEPA assessed creosote exposure using the geometric mean and maximum exposures for each scenario.

**Comment:** The Bookbinder (2001) study is the best available creosote worker exposure study, and most of the limitations identified are minor correctable issues and not critical to its utility in assessing exposure. It is unclear if the exposure assumptions from PHED are relevant to creosote workers given the unique methods in which creosote is applied and used. Exposure assumptions employed for all scenarios include: body weight = 70 kg; exposure frequency = 250 days/year; exposure duration = 40 years; dermal absorption fraction = 0.5 (unitless). More precise values for many of these default values can be obtained from the registrants for the most important exposures. As a preliminary (screening level) risk assessment, EPA should focus on characterizing the risks to these most exposed workers rather than all possible and essentially minor uses of the product and use probabilistic modeling to address the uncertainty and variation present in all of these exposure values. Additionally, and despite USEPA's statement to the contrary, the dermal absorption for BaP has been well-studied and is well below the value of 50% assumed in the risk assessment. An alternate absorption factor based on the compound or the mixture should be selected and used to assess worker risk.

The suggested options for improving the risk assessment include:

1. Reduce the number of occupational exposure scenarios (focus on worker scenario with highest potential exposures and actual data). If the risks associated with these scenarios are negligible, then risks from exposures that are lower are unlikely to be significant

2. Refine exposure assumptions, especially for dermal absorption, as suggested above. In a perfused pig ear assay (dermal structure similar to humans), the geometric mean dermal absorption of BaP in coal tar was approximately 0.16%, ranging from <0.001% to 1%. The geometric mean dermal absorption obtained for all carcinogenic PAHs in creosote combined was 0.22%, ranging from <0.001% to approximately 2.4% (VanRooij *et al.*, 1995). Dermal absorption of non-carcinogenic PAHs ranged from approximately 1% to 20%. Data indicate an inverse correlation between % absorbed and molecular weight (Figure 2), which reflects the fact that it is more difficult for large molecules to perfuse through skin than smaller ones. The pig ear model results for the absorption of pyrene *in situ* compared well to those measured for humans occupationally exposed to pyrene *in vivo* (VanRooij *et al.*, 1995), thereby providing validation for the dermal absorption values obtained from the *in situ* pig ear model while rat skin is acknowledged to be more permeable than humans and not a good model for human dermal absorption.

3. Use probabilistic (Monte Carlo) methods to address uncertainty and variability in exposure assumptions and all other parameters for which variability exists in accordance with current USEPA policy and accepted practice to the range and effect of uncertainty on the risk estimates for creosote (USEPA, 1997).

4. Use probabilistic (Monte Carlo) to address uncertainty and variability in toxicity assessment. For example, the oral potency factors for several studies of creosote or its constituent components (*i.e.*, B(a)P) or the RfCs for creosote or its constituent components (*i.e.*, naphthalene) could be characterized as a range that includes all relevant values.

We recommend that USEPA pursue all four options. The impact of correcting the dermal absorption factor alone should improve the cancer risk estimates by approximate **25- to 250-fold**. Incorporation of Monte Carlo methods should also contribute an additional improvement of approximately **3- to 30-fold**. Dermal doses from the Bookbinder (2001) study are lognormally distributed. The 95% percentile of this distribution is considerably lower than the maximum value used by USEPA for all workers. It is not realistic to assume that a worker is going to be exposed to the maximum concentration throughout a 40-year lifetime, particularly when these estimates are likely skewed due to the presence of outliers. Information regarding occupational tenure and frequency and duration of daily exposure for creosote workers would more fully and accurately characterize the distribution of exposure durations than the default assumptions currently adopted by USEPA. As a matter of science, it is also inappropriate to conduct a sensitivity analysis on the risk assessment while ignoring the parameters that are likely to be the largest source of uncertainty to the predicted risks (*i.e.*, toxicity criteria). Running sensitivity analysis twice (including and excluding toxicity value

contributions to variation) could be done to illustrate the importance of this issue in the assessment of overall risk and uncertainty.

## 5.0 CONCLUSIONS

Overall, *The Sapphire Group, Inc.* believes that the current draft USEPA risk assessment for creosote overstates the likely cancer risk by a factor ranging from **2,000- to 2,000,000-fold** simply based on three main areas of concern (*i.e.*, 30-300-fold associated with the slope factor, 25-250-fold based on an incorrect dermal absorption rate, and 3-30-fold by using a largely deterministic approach as opposed to Monte Carlo modeling to address uncertainty in exposure estimates). The non-cancer risk is also overstated by a **10- to 1,000-fold** based on assumptions used (*i.e.*, 3-30-fold for the unrefined uncertainty factor, and 3-30-fold by again using a largely deterministic approach as opposed to Monte Carlo modeling to address uncertainty in exposure estimates). Developing and using *de novo* RfC and RfD values as well as a cancer potency factor developed for the mixtures and addressing the other issues would improve the reliability and reduce the uncertainty of the risk assessment by addressing the actual product of concern as opposed to surrogate chemicals and default exposure assumptions with all the uncertainty inherent in those decisions. Additional improvements in the risk estimates would be achievable by examining and incorporating changes in other less critical toxicity and exposure variables (*i.e.*, duration and frequency of exposure, skin area exposed, inhalation rates). We recommend revising the risk assessment developed by USEPA along the lines discussed above, and anticipate having an example to share with EPA of the impact of the key issues on the outcome of the risk assessment.

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